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### (54) Suspension aerosol formulations

(57) A suspension aerosol formulation comprising a therapeutically effective amount of micronized drug selected from pirbuterol acetate and pirbuterol hydrochloride, and a propellant comprising HFC 227 the formulation being substantially free of perfluorinated surfactant.

A suspension aerosol formulation comprising a therapeutically effective amount of micronised albuterol sulphate and HFC 227 as substantially the only propellant.

**Description**

This invention relates to pharmaceutical aerosol formulations and in particular to pharmaceutical suspension aerosol formulations containing pibuterol, or albuterol sulfate and, as a propellant, HFC 227.

5 Pharmaceutical suspension aerosol formulations currently use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane, dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation.

10 Chlorofluorocarbons (CFCs), however, have been implicated in the destruction of the ozone layer and their production is being phased out. Hydrofluorocarbon 134a (HFC 134a, 1,1,1,2-tetrafluoroethane) and hydrofluorocarbon 227 (HFC 227, 1,1,1,2,3,3-heptafluoropropane) are viewed as being more ozone friendly than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor pressures suitable for use in aerosols.

15 Patent Applications WO 91/11495 and WO 91/11496 (both by Weil) describe pharmaceutical suspension aerosol formulations comprising a medicinal agent, optionally a surfactant, and a propellant mixture containing 1,1,1,2,3,3-heptafluoropropane and one or more additional components, e.g., pentane, butane, propellant 134a, propellant 11, propellant 125, or propellant 152a.

European Patent Office Publication 0 384 371 (Heiskel) describes solution aerosols in which 1,1,1,2,3,3-heptafluoropropane or its mixture with propane, butane, isobutane, dimethyl ether, or 1,1-difluoroethane serves as the propellant. The application does not, however, disclose suspension aerosols or pharmaceutical aerosol formulations.

20 European Patent Application 89.312270.5 (Purewal et al.) discloses, inter alia, aerosol formulations comprising a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent, and at least one compound having higher polarity than 1,1,1,2-tetrafluoroethane.

25 U.S. Pat. No. 2,868,691 (Porush et al.) discloses aerosol formulations comprising a medicament, a halogenated lower alkane propellant, and a cosolvent which assists in dissolving the medicament in the propellant. The chemical formula for the propellant given in Col. 2, lines 6-16, generically embraces HFC 134a and HFC 227. Examples of cosolvents disclosed include ethanol and diethyl ether.

30 U.S. Pat. No. 3,014,844 (Thiel et al.) discloses aerosol formulations comprising a micronized medicament, a halogenated lower alkane propellant and a surface-active agent to assist in the suspension of the medicament in the propellant. The chemical formula for the propellant given in Col. 4, lines 17-28, generically embraces HFC 134a and HFC 227.

35 Patent Application WO 90/01454 (Greenleaf et al.) discloses aerosol compositions having HFC 134a as the propellant and comprising a medicament coated with a non-perfluorinated surface active dispersing agent. This application describes control formulations containing only HFC 134a and 0.866 percent by weight of a drug.

40 Abuterol sulfate is a relatively selective beta-2 adrenergic bronchodilator. It is available in a variety of dosage forms including tablets, syrups and formulations suitable for inhalation. For example, VENTOLIN™ Inhalation Aerosol (commercially available from Allen & Hansburys) is a metered dose aerosol unit containing a microcrystalline suspension of albuterol (free base) in propellant (a mixture of trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. VENTOLIN ROTOCAPS™ for Inhalation (commercially available from Allen & Hansburys) contain a mixture of microfine albuterol sulfate with lactose and are intended for use with a specially designed device for inhaling powder. VENTOLIN™ Solution for Inhalation (commercially available from Allen & Hansburys) is an aqueous solution of albuterol sulfate intended for use with a nebulizer.

45 Pibuterol acetate is a relatively selective beta-2 adrenergic bronchodilator. MAXAIR™ Inhaler (commercially available from 3M Pharmaceuticals, St. Paul, Minnesota) is a metered dose aerosol unit containing a fine-particle suspension of pibuterol acetate in the propellant mixture of trichloromonofluoromethane and dichlorodifluoromethane, with sorbitan trioleate.

50 This invention provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate and HFC 227 as substantially the only propellant. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate, from about 0.1 to about 15 percent by weight of ethanol, and HFC 227 as substantially the only propellant. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate, from about 5 to 15 percent by weight of ethanol, from about 0.05 to about 0.5 percent by weight of a surfactant selected from the group consisting of oleic acid and sorbitan trioleate, and HFC 227 as substantially the only propellant.

55 In another aspect this invention provides suspension aerosol formulations comprising a therapeutically effective amount of micronized pibuterol acetate and a propellant comprising HFC 227, the formulation being substantially free of perfluorinated surfactant. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized pibuterol acetate, about 0.1 to about 12 percent by weight of ethanol, and a propellant comprising HFC 227. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized pibuterol acetate, about 5 to about 12 percent by weight of ethanol, about 0.05 to about 0.5 percent by weight of oleic acid, and a propellant comprising HFC 227.

This invention also provides an aerosol canister containing a formulation as described above in an amount sufficient to provide a plurality of therapeutically effective doses of the drug. Also provided is a method of preparing a formulation as described above, comprising the steps of: (i) combining an amount of the drug sufficient to provide a plurality of therapeutically effective doses and the propellant in an amount sufficient to propel from an aerosol canister a plurality of therapeutically effective doses of the drug; and (ii) dispersing the drug in the propellant. This invention further provides a method of treating a mammal having a condition capable of treatment by inhalation, comprising the step of administering by inhalation a formulation as described above to the mammal.

This invention also provides a method for inducing bronchodilation in a mammal, comprising administering to the mammal a formulation as described above by inhalation.

The term "suspension aerosol formulation" as used herein refers to a formulation in which the drug is in particulate form and is substantially insoluble in the propellant.

Amounts expressed herein in terms of percent refer to percent by weight based on the total weight of the formulation.

The formulations of the invention that consist essentially of drug and a propellant contain drug and propellant in relative amounts such that a formulation suitable for aerosol administration is obtained without the need for additional components. Such formulations preferably contain less than an effective stabilising amount of surfactant and more preferably are substantially free of surfactant and other components.

The formulations of the invention contain a drug in a therapeutically effective amount, that is, an amount such that the drug can be administered as an aerosol (e.g., topically or by oral or nasal inhalation) and cause its desired therapeutic effect with one dose, or less preferably several doses, from a conventional valve, e.g., a metered dose valve. "Amount" as used herein refers to quantity or to concentration as appropriate to the context. The amount of a drug that constitutes a therapeutically effective amount varies according to factors such as the potency, efficacy, and the like, of the particular drug, on the route of administration of the formulation, and on the device used to administer the formulation. A therapeutically effective amount of a particular drug can be selected by those of ordinary skill in the art with due consideration of such factors. Particularly in formulations of the invention intended for oral inhalation into the lungs, the drug is preferably micronized, i.e., about 90 percent or more of the particles have a diameter of less than about 10 microns, in order to assure that the particles can be inhaled into the lungs.

The particular amount of drug that will remain suspended in a formulation of the invention for a time sufficient to allow reproducible dosing of the drug depends to some extent on the nature of the particular drug, e.g., its density, and on the particular propellant used in the formulation. Generally, however, it has been found that when drug concentrations of less than about 0.1 percent are used in a formulation of the invention the drug flocculates to some degree but generally does not settle or cream to the extent that the suspension becomes unsuitable for use as an aerosol formulation, e.g., in a metered dose inhaler. Therefore as regards drug concentration such formulations are acceptably homogeneous.

When drug concentrations greater than about 0.1 percent but less than about 0.5 percent are used in a formulation of the invention it is sometimes seen that the drug flocculates considerably in the formulation and therefore might have an increased tendency to cream or settle. As discussed below in connection with the propellant component of the formulations of the invention, in these instances it is preferable to select the propellant in a manner that minimizes creaming and settling of the drug in order to assure that the formulation is acceptably homogeneous as regards drug concentration.

As drug concentration increases, e.g., beyond about 0.5 percent, the tendency of the drug to flocculate generally increases also. However, the volume occupied by the flocculated drug also increases and the flocculated drug begins to occupy substantially all of the volume of the formulation. In such instances the flocculated drug often shows a lesser tendency to cream or settle. As regards drug concentration such formulations are acceptably homogeneous.

Generally the concentration of the drug in a formulation of the invention is preferably less than about 0.1 percent, more preferably less than about 0.08 percent, and most preferably less than about 0.05 percent. Accordingly, it is preferred according to this invention that the drug have a potency such that concentrations less than about 0.1 percent, more preferably less than about 0.08 percent, and most preferably less than about 0.05 percent, are therapeutically effective. Drugs for use in the formulations of the invention include albuterol, pirbuterol, and pharmaceutically acceptable salts and solvates thereof, particularly albuterol sulfate and pirbuterol acetate.

The propellant in a formulation of the invention can be HFC 134a, HFC 227, or a mixture thereof in any proportion. The propellant is present in an amount sufficient to propel a plurality of doses from a metered dose inhaler. The density of HFC 134a differs from the density of HFC 227. Therefore the density of the propellant can be adjusted within limits by using mixtures of HFC 134a and HFC 227 in order to accommodate the density of the drug. It is sometimes preferred that the propellant be selected such that the propellant density is as closely matched as possible to the drug density in order to minimize tendencies for the drug to settle or cream, particularly when drug concentration is greater than 0.1 percent or when the drug concentration is between about 0.1 percent and about 0.5 percent.

The pirbuterol acetate formulations of the invention contain a therapeutically effective amount of pirbuterol acetate. Preferably, the pirbuterol acetate constitutes about 0.4 to about 1.0 percent by weight, more preferably about 0.45 to about 0.9 percent by weight, of the aerosol formulation. Preferably the pirbuterol acetate is micronized.

Ethanol can optionally be included in a pirbuterol acetate aerosol formulation of the invention. When ethanol is present it constitutes from about 0.1 to about 12 percent by weight, preferably from about 5 to about 12 percent by weight

of the aerosol formulation. In another aspect of this invention ethanol preferably constitutes from about 2 to about 8 percent by weight of the formulation. Oleic acid can optionally be included in a pibuterol acetate formulation of the invention that includes ethanol. When oleic acid is present it constitutes about 0.01 to about 0.5 percent by weight of the formulation.

5       Typically the propellant constitutes the remainder of the weight of the formulation once the pibuterol acetate and the optional ethanol and oleic acid are accounted for. Accordingly the propellant is generally present in an amount of at least about 85 percent by weight based on the total weight of the formulation. The propellant in a pibuterol acetate formulation of the invention comprises HFC 227, preferably as substantially the only propellant. However, one or more other propellants such as propellant 142b (1-chloro-1,1-difluoroethane), HFC 134a, and the like can be used, preferably in pibuterol acetate formulations of the invention containing ethanol.

10      Preferred pibuterol acetate formulations of the invention exhibit substantially no growth in particle size or change in crystal morphology of the pibuterol acetate over a prolonged period, are substantially and readily redispersible, and upon redispersion do not flocculate so quickly as to prevent reproducible dosing of pibuterol acetate.

15      The albuterol sulfate formulations of the invention contain a therapeutically effective amount of micronized albuterol sulfate. Preferably micronized albuterol sulfate constitutes about 0.2 to about 0.5 percent by weight, more preferably from about 0.35 to about 0.42 percent by weight of the aerosol formulation.

20      Ethanol can optionally be included in such an albuterol sulfate formulation of the invention. When ethanol is present it constitutes from about 0.1 to about 20 percent by weight, preferably from about 5 to about 15 percent by weight of the formulation. A surfactant selected from the group consisting of oleic acid and sorbitan trioleate can also optionally be included in the formulation when the formulation also includes ethanol. When a surfactant is present it constitutes about 0.01 to about 0.5 percent by weight of the aerosol formulation. Albuterol sulfate formulations of the invention that do not contain ethanol are preferably substantially free of perfluorinated surfactant.

25      Certain preferred albuterol sulfate suspension aerosol formulations of the invention comprise HFC 227 as substantially the only propellant. Typically the propellant constitutes the remainder of the weight of the formulation once the albuterol sulfate and the optional surfactant and/or ethanol are accounted for. Accordingly the propellant is generally present in an amount of at least about 75 percent by weight based on the total weight of the formulation.

30      Preferred albuterol sulfate formulations of the invention exhibit substantially no growth in particle size or change in crystal morphology of the albuterol sulfate over a prolonged period, are substantially and readily redispersible, and upon redispersion do not flocculate so quickly as to prevent reproducible dosing of albuterol sulfate.

35      Generally the formulations of the invention can be prepared by combining (i) the drug in an amount sufficient to provide a plurality of therapeutically effective doses; and (ii) the propellant in an amount sufficient to propel a plurality of doses from an aerosol canister; and dispersing the drug in the propellant. The drug can be dispersed using a conventional mixer or homogenizer, by shaking, or by ultrasonic energy. Bulk formulation can be transferred to smaller individual aerosol vials by using valve to valve transfer methods or by using conventional cold-fill methods.

40      The pibuterol acetate suspension aerosol formulations of this invention can be prepared by combining the pibuterol acetate and the propellant and then dispersing the pibuterol acetate in the propellant using a conventional mixer or homogenizer. Pibuterol acetate, however, is somewhat soluble in ethanol alone. Accordingly, when oleic acid and/or ethanol are included in the formulation, it is preferred that the pibuterol acetate be first placed in an aerosol vial. A mixture of the propellant, oleic acid and/or ethanol can then be added, and the pibuterol acetate dispersed in the mixture.

45      The albuterol sulfate suspension aerosol formulations of this invention can be prepared by combining the albuterol sulfate and the propellant and dispersing the albuterol sulfate in the propellant using a conventional mixer or homogenizer. When a surfactant and/or ethanol are included in the formulation, they can be added to the propellant along with the albuterol sulfate.

50      Aerosol canisters equipped with conventional valves, preferably metered dose valves, can be used to deliver the formulations of the invention. It has been found, however, that selection of appropriate valve assemblies for use with aerosol formulations is dependent upon the particular surfactants or adjuvants used (if any), on the propellant, and on the particular drug being used. Conventional neoprene and buna valve rubbers used in metered dose valves for delivering conventional CFC formulations often have less than optimal valve delivery characteristics and ease of operation when used with formulations containing HFC 134a or HFC 227. Moreover, conventional CFC formulations generally contain a surfactant in part as a lubricant for the valve stem. Some formulations of the invention, however, do not contain a surfactant or a lubricant. Therefore certain formulations of the invention are preferably dispensed via a valve assembly wherein the diaphragm is fashioned by extrusion, injection molding or compression molding from a thermoplastic elastomeric material such as FLEXOMER™ DFDA 1137 NT7 polyolefin, FLEXOMER™ DFDA 1138 NT polyolefin, FLEXOMER™ DEFD 8923 NT polyolefin, FLEXOMER™ GERS 1085 NT polyolefin, FLEXOMER™ DFDA 1163 NT7 polyolefin, FLEXOMER™ 1491 NT7 polyolefin, FLEXOMER™ 9020 NT7 polyolefin, FLEXOMER™ 9042 NT polyolefin (Union Carbide), C-FLEX™ thermoplastic elastomer R70-001, C-FLEX™ thermoplastic elastomer R70-051, C-FLEX™ thermoplastic elastomer R70-041, C-FLEX™ thermoplastic elastomer R70-085, C-FLEX™ thermoplastic elastomer R70-003, or C-FLEX™ thermoplastic elastomer R70-026 (Concept Polymer Technologies), or a blend of two or more thereof.

Conventional aerosol canisters, e.g., those of aluminum, glass, stainless steel, or polyethylene terephthalate, can be used to contain a formulation of the invention.

The formulations of the invention can be delivered to the lung by oral inhalation in order to effect bronchodilation or in order to treat a condition susceptible of treatment by inhalation, e.g., asthma, chronic obstructive pulmonary disease.

5 The formulations of the invention can also be delivered by nasal inhalation in order to treat, e.g., allergic rhinitis, rhinitis, or diabetes, or they can be delivered via topical (e.g., buccal) administration in order to treat, e.g., angina or local infection.

The following Examples are provided to illustrate the invention. All parts and percentages are by weight unless otherwise indicated.

10 Example 1

A 1.35 g portion of micronized pirbuterol acetate, 15.0 g of ethanol and 30 mL of glass beads were placed in a 120 mL (4 ounce) glass aerosol vial. The vial was sealed with a continuous valve, pressure filled with approximately 133 g of HFC 227 and then shaken on a paint shaker for 10 minutes. The resulting formulation contained 0.9 percent by weight 15 of pirbuterol acetate and 10.0 percent by weight of ethanol. The dispersion was transferred into 10 mL aerosol vials which were sealed with 25  $\mu$ L Sprymiser™ Aerosol Valves (available from Neotechnic Engineering Ltd.).

This formulation was tested for its ability to deliver a consistent dose throughout the "life" of the aerosol by determining the amount of pirbuterol acetate delivered per shot for shots 1, 2, 101, 102, 201, 202, 301 and 302. The amount delivered per shot was determined using the assay described below. The results are shown in the table below.

20 A firing disk was placed in a 100 mL beaker and submerged in about 30 mL of diluent (55 parts methanol/ 45 parts 0.1 percent phosphoric acid, v/v). The vial was shaken, inserted into the firing disk, and actuated. The valve and valve stem were rinsed into the beaker with additional diluent. The solution in the beaker was quantitatively transferred to a 100 mL volumetric flask which was then brought to volume with additional diluent. The amount of pirbuterol acetate in the solution was determined using high performance liquid chromatography.

25

$\mu$ g Pirbuterol Acetate				
	# of shots	Vial 1	Vial 2	Vial 3
30	1	415.4	379.3	360.1
	2	378.7	361.0	322.1
35	101	404.0	380.4	374.7
	102	352.0	389.1	337.9
40	201	376.8	380.6	337.5
	202	371.5	357.8	328.6
45	301	288.2	408.8	361.1
	302	193.4	364.5	341.0

Example 2

A 11.7 g portion of pirbuterol acetate was placed in a beaker then chilled in a dry ice/trichlorofluoromethane bath. A portion of prechilled HFC 227 was added to the beaker and the resulting slurry was mixed at high speed with a VIRTIS™

50 Model 45 mixer for at least 3 minutes. The dispersed concentrate was then transferred to a glass bottle and enough prechilled HFC 227 was added to bring the total net content weight to 1300 g. The resulting formulation contained 0.9 percent by weight of pirbuterol acetate. The formulation was transferred to a cold filling system and filled into 10 mL aluminum aerosol vials which were then sealed with 25  $\mu$ L valves. The formulation was deemed to be suitable for use in connection with a metered dose inhaler.

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Example 3

A 11.7 g portion of micronized pirbuterol acetate, 3.0 g of oleic acid and 60 g of ethanol were placed in a beaker and homogenized for at least 3 minutes. The resulting slurry was transferred to a tared glass bottle and enough ethanol

5 was added to bring the total weight of the concentrate to 144.7 g. The concentrate was chilled then placed along with 1155 g of prechilled HFC 227 into a prechilled cold filling system. The formulation was filled into 10 mL aluminum aerosol vials which were then sealed with 25  $\mu$ L Spraymiser™ valves. The resulting formulation contained 0.90 percent by weight of pirbuterol acetate, 0.23 percent by weight of oleic acid and 10.0 percent by weight of ethanol. The formulation was deemed to be suitable for use in connection with a metered dose inhaler.

In Examples 4 and 5 below, respirable fraction is determined using the test method described below.

#### Respirable Fraction

10 In this assay the respirable fraction (the percent by weight of particles having an aerodynamic particle size of less than 4.7 microns) of the aerosol suspension is determined using an Anderson Cascade Impactor (available from Anderson Sampler Inc.; Atlanta, GA).

15 The aerosol vial to be tested is primed five times. The valve and valve stem are then cleaned with methanol and dried with compressed air. The aerosol vial and a clean, dry actuator are coupled to the glass throat attached to the top of the impactor using an appropriate firing adaptor. The calibrated vacuum pump (28.3 L/min) attached to the cascade impactor is turned on. A total of 20 sprays is delivered into the cascade impactor by repeatedly shaking the vial, seating it in the actuator and immediately delivering a single spray. The time between sprays is approximately 30 seconds. The cascade impactor is disassembled and each component is rinsed separately with diluent (55 parts methanol mixed with 45 parts of 0.1 percent aqueous phosphoric acid, v/v). Each solution is analyzed for pirbuterol acetate content using 20 high performance liquid chromatography. The respirable fraction is calculated as follows:

$$\% \text{ respirable} = \frac{\text{drug recovered from plates 3-7} \times 100}{\text{total drug} - \text{drug recovered from recovered actuator and valve}}$$

25 Example 4

A 1.35 g portion of micronized pirbuterol acetate and 25 mL of glass beads were placed in a 120 mL (4 ounce) glass aerosol vial. The vial was sealed with a continuous valve, pressure filled with approximately 150 g of HFC 227 and then 30 shaken for at least 10 minutes on an automatic shaker. The resulting formulation contained 0.9 percent by weight of pirbuterol acetate. The vial was then charged with 150 psi ( $1 \times 10^6$  N/m<sup>2</sup>) nitrogen to aid in product transfer to smaller vials. The formulation was transferred to 10 mL aluminum aerosol vials sealed with continuous valves by using a valve to valve transfer button. The vials were then chilled in dry ice then the continuous valves were removed and the vials sealed with 25  $\mu$ L metering valves. Using the method described above, the respirable fraction was determined in duplicate 35 for two separate vials. Values of 59.1 percent and 54.8 percent were obtained for vial 1. Values of 53.9 percent and 49.3 percent were obtained for vial 2.

#### Example 5

40 A 1.35 g portion of micronized pirbuterol acetate, 15.0 g of ethanol and 25 mL of glass beads were placed in a 120 mL (4 ounce) glass aerosol vial. The vial was sealed with a continuous valve, pressure filled with approximately 134 g of HFC 227 and then shaken on an automatic shaker for at least 10 minutes. The resulting formulation contained 0.9 percent by weight of pirbuterol acetate and 10 percent by weight of ethanol. Individual 10 mL aerosol vials were filled and sealed with 25  $\mu$ L metering valves using the method described in Example 11. Using the test method described 45 above, the respirable fraction was determined in duplicate for two separate vials. Values of 34.9 percent and 32.5 percent were obtained for vial 1. Values of 31.7 percent and 31.3 percent were obtained for vial 2.

In Examples 6 and 7 below respirable fraction is determined using the test method described above but using a diluent of 45 parts by volume methanol and 55 parts by volume of 0.1 percent aqueous phosphoric acid.

#### Example 6

50 A 0.60 g portion of micronized albuterol sulfate and 25 mL of glass beads were placed in a 120 mL (4 ounce) glass aerosol vial. The vial was sealed with a continuous valve and then pressure filled with approximately 150 g of HFC 227. The vial was shaken to disperse the albuterol sulfate. The resulting formulation contained 0.4 percent by weight of 55 albuterol sulfate. The formulation was transferred to 10 mL aluminum aerosol vials sealed with continuous valves by using a valve to valve transfer button. The vials were chilled in dry ice then the continuous valves were removed and the vials were sealed with 25  $\mu$ L metering valves. Using the method described above, the respirable fraction was determined in duplicate for two separate vials. Values of 69.3 percent and 60.6 percent were obtained for vial 1. Values of 64.0 percent and 63.0 percent were obtained for vial 2.

Example 7

5 A 0.60 g portion of micronized albuterol sulfate, 0.75 g of oleic acid, 22.5 g of ethanol and 25 mL of glass beads were placed in a 120 mL (4 ounce) glass aerosol vial. The vial was sealed with a continuous valve and then pressure filled with approximately 126 g of HFC 227. The vial was shaken to disperse the albuterol sulfate. The resulting formulation contained 0.40 percent by weight of albuterol sulfate, 0.50 percent by weight of oleic acid and 15.0 percent by weight of ethanol. Individual aerosol vials were filled and fitted with 25  $\mu$ L metering valves using the method described in Example 13. Using the test method described above, the respirable fraction was determined in duplicate for two separate vials. Values of 28.0 percent and 22.0 percent were obtained for vial 1. Values of 27.1 percent and 28.8 percent were obtained for vial 2.

10

Example 8

15 A suspension aerosol formulation containing 0.37 percent by weight of albuterol sulfate, 0.10 percent by weight of sorbitan trioleate (commercially available under the trade designation Span 85), 9.95 percent by weight of ethanol and 89.58 percent by weight of HFC 227 was prepared. The formulation was deemed to be suitable for use in connection with a metered dose inhaler.

Example 9

20 A 4.5 g portion of ethanol was placed in a 125 mL (4 ounce) glass aerosol vial. The vial was sealed with a continuous valve then pressure filled with 147 g of HFC 227. Portions (approximately 225 mg) of micronized pirbuterol acetate were weighed into 6 separate 15 mL glass aerosol vials. A 5 mL portion of glass beads was added to each vial and the vials were sealed with continuous valves. Each vial was then pressure filled with approximately 19.8 g of the ethanol/HFC 25 227 solution. The resulting formulation contained 3 percent by weight of ethanol and 0.9 percent by weight of pirbuterol acetate. The vials were then shaken in a paint shaker for 15 minutes. The vials were cooled in dry ice, the continuous valves were removed and the contents poured into separate 15 mL aluminum aerosol vials. The aluminum vials were sealed with 25  $\mu$ L valves equipped with diaphragms fabricated from C-Flex R-70-051 and tanks seals fabricated from DB218. Using the test method described above, the respirable fraction was determined for two separate vials. Values of 59.8% and 52.8% were obtained. Using the test method described above, the ability of the formulation to deliver a consistent dose throughout the "life" of the aerosol was determined. The results are shown in the table below. The values are the average for the indicated shots.

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$\mu$ g Pirbuterol Acetate/shot		
Shot #	Vial 1	Vial 2
1 & 2	279.4	304.6
101 & 102	197.1	329.9
201 & 202	294.9	478.1
301 & 302	295.8	294.1
401 & 402	269.6	350.3

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Example 10

50 Using the general method of Example 9, 6 vials of a formulation containing 5 percent by weight of ethanol and 0.9 percent by weight of pirbuterol acetate were prepared. Using the method described above, the respirable fraction was determined for two separate vials. Values of 48.2% and 43.5% were obtained. Using the method described above, the ability of the formulation to deliver a consistent dose throughout the "life" of the aerosol was determined. The results are shown in the Table below.

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µg Pirbuterol Acetate/shot		
Shot #	Vial 1	Vial 2
1 & 2	263.9	288.5
101 & 102	283.5	325.4
201 & 202	300.6	367.2
301 & 302	330.7	306.6
401 & 402	312.8	270.5

## Claims

20 1. A suspension aerosol formulation comprising a therapeutically effective amount of micronized drug selected from pirbuterol acetate and pirbuterol hydrochloride, and a propellant comprising HFC 227 the formulation being substantially free of perfluorinated surfactant.

25 2. A formulation as claimed in Claim 1 in which the drug is pirbuterol acetate.

25 3. A formulation as claimed in Claim 2 comprising from 0.1 to 12 percent by weight of ethanol.

4. A formulation as claimed in Claim 3 comprising from 2 to 8 percent by weight of ethanol.

30 5. A formulation as claimed in Claim 3 or Claim 4 comprising from 0.05 to 0.5 percent by weight of oleic acid.

6. A suspension aerosol formulation comprising a therapeutically effective amount of micronised albuterol sulfate and HFC 227 as substantially the only propellant.

35 7. A formulation as claimed in Claim 6 comprising from 5 to 15 percent by weight of ethanol.

8. A formulation as claimed in Claim 7 comprising from 0.05 to 0.5 percent by weight of a surfactant selected from oleic acid and sorbitan trioleate.

40 9. A metered dose aerosol canister containing a formulation as claimed in any preceding Claim in an amount sufficient to provide a plurality of therapeutically effective doses of the drug.

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